Comprehensive methylome map of lineage commitment from haematopoietic progenitors.

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Public Summary:
Having charted the occurrence of a common chemical change that takes place while stem cells decide their fates and progress from precursor to progeny, we has produced the first-ever epigenetic landscape map for tissue differentiation. The researchers, using blood-forming stem cells from mice, focused their investigation specifically on an epigenetic mark known as methylation. This change is found in one of the building blocks of DNA, is remembered by a cell when it divides, and often is associated with turning off genes. Employing a customized genome-wide methylation-profiling method dubbed CHARM (comprehensive high-throughput arrays for relative methylation), we analyzed 4.6 million potentially methylated sites in a variety of blood cells from mice to see where DNA methylation changes occurred during the normal differentiation process. The team chose the blood cell system as its model because it's well-understood in terms of cellular development. We looked at eight types of cells in various stages of commitment, including very early blood stem cells that had yet to differentiate into red and white blood cells. We also looked at cells that are more committed to differentiation: the precursors of the two major types of white blood cells, lymphocytes and myeloid cells. Finally, we looked at older cells that were close to their ultimate fates to get more complete pictures of the precursor-progeny relationships — for example, at white blood cells that had gone fairly far in T-cell lymphocyte development. (Lymphoid and myeloid constitute the two major types of progenitor blood cells.) One of the surprising finds was how widely DNA methylation patterns vary in cells as they differentiate. It wasn't a boring linear process, instead, there are these waves of change during the development of these cell types. The data shows that when all is said and done, the lymphocytes had many more methylated genes than myeloid cells. However, on the way to becoming highly methylated, lymphocytes experience a huge wave of loss of DNA methylation early in development and then a regain of methylation. The myeloid cells, on the other hand, undergo a wave of increased methylation early in development and then erase that methylation later in development. Because the data seem to indicate discreet stages of cell differentiation characterized by waves of changes in one direction and subsequent waves in another, cell types conceivably could be redefined according to epigenetic marks that will provide new insights into both normal development and disease processes. Leukemias and lymphomas likely involve disruptions of the epigenetic landscape. As epigenetic maps such as this one begin to get fleshed out by us and others, they will guide our understanding of why those diseases behave the way they do, and pave the way for new therapies.

Scientific Abstract:
Epigenetic modifications must underlie lineage-specific differentiation as terminally differentiated cells express tissue-specific genes, but their DNA sequence is unchanged. Haematopoiesis provides a well-defined model to study epigenetic modifications during cell-fate decisions, as multipotent progenitors (MPPs) differentiate into progressively restricted myeloid or lymphoid progenitors. Although DNA methylation is critical for myeloid versus lymphoid differentiation, as demonstrated by the myeloerythroid bias in Dnmt1 hypomorphs, a comprehensive DNA methylation map of haematopoietic progenitors, or of any multipotent/oligopotent lineage, does not exist. Here we examined 4.6 million CpG sites throughout the genome for MPPs, common lymphoid progenitors (CLPs), common myeloid progenitors (CMPs), granulocyte/macrophage progenitors (GMPs), and thymocyte progenitors (DN1, DN2, DN3). Marked epigenetic plasticity accompanied both lymphoid and myeloid restriction. Myeloid commitment involved less global DNA methylation than lymphoid commitment, supported functionally by myeloid skewing of progenitors following treatment with a DNA methyltransferase inhibitor. Differential DNA methylation correlated with gene expression more strongly at CpG island shores than CpG islands. Many examples of genes and pathways not previously known to be involved in choice between lymphoid/myeloid differentiation have been identified, such as Arl4c and Jdp2. Several transcription factors, including Meis1, were methylated and silenced during differentiation, indicating a role in maintaining an undifferentiated state. Additionally, epigenetic modification of

modifiers of the epigenome seems to be important in haematopoietic differentiation. Our results directly demonstrate that modulation of DNA methylation occurs during lineage-specific differentiation and defines a comprehensive map of the methylation and transcriptional changes that accompany myeloid versus lymphoid fate decisions.
